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Scott F. Gilbert. (1984). "Intellectual Traditions In The Life Sciences: II. Stereocomplementarity". *Perspectives In Biology And Medicine*. Volume 28, Issue 1. 18-34. DOI: 10.1353/pbm.1984.0024
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Perspectives in Biology and Medicine, Volume 28, Number 1, Autumn 1984, pp. 18-34 (Article)

Published by The Johns Hopkins University Press
DOI: 10.1353/pbm.1984.0024

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INTELLECTUAL TRADITIONS IN THE LIFE SCIENCES. II. STEREOCOMPLEMENTARITY

SCOTT F. GILBERT* and JASON P. GREENBERG†

Each generation of biological and medical researchers is subtly guided by intellectual traditions of which it is largely unaware. In the first paper of this series [1], it was shown that the divergence of biochemistry and molecular biology during the middle of this century was due to rival traditions concerning the physical nature of life. In this study, we will discuss the research at the turn of the present century which formulated what has become the central theoretical assumption of contemporary biochemistry, cell biology, physiology, molecular biology, pharmacology, developmental biology, and endocrinology, namely, *stereocomplementarity*.

It is hard to imagine any phenomenon on the cellular or molecular level which is not governed by lock-and-key stereocomplementarity. The “central dogma” of DNA replication, RNA transcription, and the translation of polypeptides is a tour-de-force of the lock-and-key principle, with certain elements (such as tRNAs and aminoacyl transferases) having multiple regions of complementarity. The proteins involved in and produced by polypeptide synthesis are also locks and keys. Stereocomplementarity has long been seen as responsible for the specificity of enzymes interacting with substrates and of antibodies interacting with antigens. Moreover, the ability of small molecules to allosterically affect the rate of enzyme catalysis and the ability of complement molecules to lyse cell membranes have been attributed to stereocomplementary binding at the nonreactive site of enzymes and antibodies, respectively.

Structural proteins similarly accomplish their functions through lock-and-key specificity. Hormone and drug receptors have specific binding sites for their respective compounds, cytoskeletal proteins form their fibers through the interactions of their respective amino acids, and the

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proteins of the extracellular matrix, such as fibronectin, often have multiple binding sites which enable them to join cells together with other matrix molecules.

The ability to form lock-and-key structures with another compound has taken on a role as the “proof” of a substance’s function. To Watson and Crick, the stereocomplementarity of the two DNA strands “suggested” its mode of replication. More recently, the observation that certain brain cells bind opium and its agonists is seen as showing that these neurons are involved in pain perception, and the observation that certain small nuclear RNA species have sequences complementary to those of the most common RNA splicing junctions has been cited as evidence that these molecules function in the RNA processing mechanism. Our entire technology for determining nucleic acid complexity and for locating, isolating, and cloning genes depends on the stereocomplementarity of nucleic acid hybridization. It is apparent, then, that we, as scientists, are very much impressed by the argument for specificity based on stereocomplementarity. Stereocomplementarity has become our major way of relating molecular structure and function, and it currently forms the basis for almost all our contemporary cellular biology and pharmacology.

The concept of lock-and-key specificity is not so much studied as assumed. It is not so much a “fact” to be learned as it is a guiding principle for researchers in numerous biomedical fields. In this essay, we will attempt (a) to trace the emergence of this principle and its entry into biology and medicine, and (b) to place the original opposition to this concept into a larger controversy which characterized early twentieth-century biology.

I

Although the lock-and-key model of enzyme catalysis is conventionally ascribed to Emil Fischer, one may readily trace the germ of the idea to Louis Pasteur’s work under Auguste Laurent. It was the beginning of the era in which chemicals were thought to be structures made of atoms. Pasteur started his work with Laurent in 1846 after the latter had confirmed the “theory of substitutions,” which, according to Pasteur, saw chemicals as “molecular edifices, in which one element could be replaced by another without disturbing the structure of the edifice; as if one were to replace, one by one, every stone of a monument by a new stone” (quoted in [2]). Laurent showed Pasteur that a pure compound which the former had crystallized had taken three distinct crystalline forms which were recognizable under the microscope. This phenomenon fascinated Pasteur, and in 1848 he submitted to the Académie des Sciences

“Recherches sur le dimorphisme,” a paper in which he listed all compounds which were known to have multiple crystalline forms [3].

Later, Pasteur studied the ability of such crystals to rotate light. Because so much was known about them, he focused his inquiries on tartaric acid and the tartrates. The German chemist Mitscherlich had discovered that, along with the common, large tartaric acid crystals found in the tartar formed by the fermentation of wine, there were on occasion smaller crystals which were called paratartaric acid (from the Latin *para*, alongside) or racemic acid (from the Latin *racemus*, grape). Mitscherlich wrote that these two acids had “the same chemical composition, the same crystal shape with the same angles, the same specific gravity, the same double refraction, and therefore the same angle between their optical axes. But the solution of the tartrate rotates the plane of polarization, while the paratartrate is inactive” (quoted in [4]). Pasteur noticed that the crystals of the tartrate and tartaric acid were hemihedral, a fact which Mitscherlich had missed. Postulating that tartaric acid and paratartaric acid were chemically different and hoping that this difference would be reflected in the crystal structure, Pasteur thought that the paratartaric acid crystals might not be hemihedral. When he examined them, he found that they were hemihedral, but half of them looked like crystals of tartaric acid and the other half were mirror images of them. Pasteur sorted these by hand and examined the groups separately. The ones which looked like tartaric acid rotated light exactly as tartaric acid did, and the mirror-image crystals rotated light exactly as strongly but in the opposite direction. When equal amounts of the two types were mixed, there was no rotation of light. Pasteur was delighted—he had made his first major discovery, at the age of 25.

In 1857 Pasteur conducted an experiment which would provide the link between his work on enantiomers and Fischer’s on enzymes. It was well known that mold grew on solutions of calcium paratartrate in warm environments. Most researchers simply discarded the contaminated preparations, but Pasteur decided to examine the changes in the ability of the solution to rotate light (its optical activity) over time. The paratartrate started as optically neutral, but as the mold grew the solution became more optically active. Pasteur showed that the mold destroyed the dextrorotatory form of the acid, leaving behind the levorotatory form. He was aware that, although many compounds made by living organisms were optically active, when produced in the laboratory the same compounds were optically neutral. Combining this with his observation that a mold selected one of the two stereoisomers of calcium paratartrate, he concluded that molecular asymmetry is central to living organisms; in his words, it “constitutes perhaps the only sharply defined difference between the chemistry of dead and of living matter” [1, p. 36].

This is part of the basis of the lock-and-key model. If living beings are

composed of asymmetric molecules and can select them from a milieu which includes both forms, this implies that organisms are capable of recognizing and constructing such molecules. Pasteur called the matrices which formed these asymmetric molecules "dissymmetric forces" [5]. Kottler [6] has speculated that Pasteur "had come to think of a dissymmetric molecule as the seat of a force which, during chemical combination in a racemic solution, differentiated between the racemic isomers according to the directions of *their* dissymmetry." Pasteur [5, p. 340] employed the following analogy: "We may think of a right-handed screw and a left-handed screw as being driven separately into identical, straight grained blocks of wood. All of the mechanical conditions of the two systems are the same. This is instantly changed when the same two screws are driven into blocks in which the fibers themselves have a right or left spiral arrangement."

So by 1852, Pasteur was already thinking in terms of some sort of stereospecificity between the dissymmetric molecule (the screw) and a dissymmetric force (the wood grain). This force was present in and characteristic of life, and it acted during the synthesis of organic compounds:

The dissimilarity of the properties of active bodies in contact with other active bodies testifies evidently to the dissymmetric disposition of the forces to which the active molecules give rise, and it is probable that mutually inverse active bodies would continue to exhibit dissimilar behavior under the influence of any agents, provided that they were dissymmetric. In order to account for the exclusive formation of molecules of a single order of dissymmetry it therefore suffices to admit that *at the moment of their grouping the elementary atoms are subjected to a dissymmetric influence*, and as all organic molecules which have arisen in analogous circumstances are identical, *this influence must be universal*. It would embrace the entire terrestrial globe. To it would be due the molecular dissymmetry of organic natural products of vegetable organisms, products which we rediscover among animals almost without alteration and where they play a mysterious role of which we do not yet have the slightest idea. [7]

Pasteur, however, had no concept of enzymes as catalysts for biochemical reactions. Quite to the contrary, Pasteur argued vehemently that the synthetic properties of an organism were a property of the intact living organism and could not exist apart from the organism. He believed that whereas yeasts could synthesize ethanol from sugars, the filtrate of crushed yeast could not. Thus, he refused to give credence to Buchner's report that yeast extract could accomplish these reactions by itself.

The concept of stereospecificity between two compounds could not be proposed until it had been demonstrated that the "forces" postulated by Pasteur were properties of particular molecules. As the century ended, there was still active controversy over whether the fermenting ability of yeast extract was due to defined chemical entities. Jager (1890) and Arthus (1896) claimed that the reactions catalyzed by this extract

operated over a distance and did not need contact with their substrates. Buchner's own opinion that he had demonstrated that the active agent of fermentation "without doubt is to be regarded as a protein" was not a unanimously shared opinion [8].

It was Emil Fischer who linked Pasteur's dissymmetric forces with protein molecules. Fischer had discovered that phenylhydrazine reacted with aldehyde groups, and in 1894 he used this technique to determine the structural configuration of hexose and pentose sugars. Moreover, that same year, he demonstrated that, whereas the dextrorotatory forms of these compounds were readily fermented by yeast extract, the levorotatory forms were not. He concluded that

among the agents used by the living cell, the principal role is played by the various albuminoid substances. They are optically active, and since they are synthesized from the carbohydrates of plants, one may well assume that the geometrical structure of their molecules, as regards their asymmetry, is fairly similar to that of the natural hexoses. On the basis of this assumption, it would not be difficult to understand that the yeast cells, with their asymmetrically-constructed agent, can only attack and ferment those kinds of sugars whose geometry is not too different from that of grape sugar. [(9); translated in (8)]

In another crucial experiment published that year, Fischer compared the action of two enzyme preparations on two enantiomeric methylglucosides which he had prepared previously. He found that the one less soluble in methyl alcohol (which he designated the alpha form) was hydrolyzed by the enzyme he called "invertin" (a yeast extract actually) but not by emulsin; the more soluble or beta form was hydrolyzed by emulsin but not by invertin.

How, then, could the specificity of the two enzymes be explained if their substrates were so similar? First, he reasoned that these two enzymes are also asymmetrically constructed molecules. Thus, he wrote, "[the enzymes'] restricted action on the glucosides may therefore be explained on the basis of the assumption that only with a similar geometrical structure can the molecules approach each other closely, and thus initiate the chemical reaction. To use a picture, I would say that the enzyme and the glucoside must fit each other like a lock and key, in order to effect a chemical action on each other" [10]. Here we have his first statement of the principle of stereocomplementarity, to which Fischer notes, "The finding that the activity of enzymes is limited by molecular geometry to so marked a degree should be of some use for physiological research."

II

We have seen that the concept of lock-and-key specificity was formulated in the cauldron of European biochemistry. As there was little

connection between chemistry, biology, and medicine at that time, it is interesting to observe how this notion entered the biological and medical provinces. Although Fischer predicted that such specificity would be useful in physiological studies, the first use of stereocomplementarity is seen in the young discipline of immunology, a field that was a meeting place of chemistry, biology, and medicine.

Paul Ehrlich focused his attention on two related biomedical problems: first, how do bacterial toxins destroy cells; and second, what is the nature of the antibody molecules that neutralize the toxin? His “side-chain” theory of immunity (1897) linked cell nutrition with cell protection and utilized the notion of stereocomplementarity to explain both the specificity of toxin action and the specificity of the antibodies produced against the toxin. Very simply put, Ehrlich viewed each cell as extending numerous side chains of protoplasm by which it could absorb various nutrients from the medium. The attachment of foodstuffs to the side chains is governed by the stereocomplementarity principle seen by the biochemists:

We are obliged to adopt the view, that the protoplasm is equipped with certain atomic groups, whose function especially consists in fixing to themselves certain food-stuffs, of importance to the cell-life. Adopting the nomenclature of organic chemistry, these groups may be designated side-chains. We may assume that the protoplasm consists of a special executive centre . . . in connection with which are nutritive side-chains, which possess a certain degree of independence, and which may differ from one another according to the requirements of the different cells. And as these side-chains have the office of attaching to themselves certain food-stuffs, we must also assume an atomic-grouping in these food-stuffs themselves, every group uniting with a corresponding combining group of a side-chain. The relationship of the corresponding groups, *i.e.* those of the food-stuff and those of the cell, must be specific. They must be adapted to one another, as, *e.g.* male and female screw (Pasteur), or as lock and key (E. Fischer). [11]

From this point of view, the toxin was considered to be a competitor for the side chains. One part of the toxin, the “haptophore,” bound to the side chain and rendered the cell vulnerable to damage by the “toxophore” portion of the toxin. The toxin could work actively or it could prevent normal food uptake. Since certain toxins affect different tissues, Ehrlich speculated that different cells had different side chains and different nutritional needs. Antibodies represented the overproduction and release of these side chains into the blood. The cell begins to make new side chains for the specific foodstuff being competed for by the toxin. The circulating toxin binds to the newly made side chains, as well. Even more of these specific side chains are then produced at an increasingly rapid rate, and the cell overcompensates by producing more side chains than it can hold. The extra side chains are released by the cell, existing in the serum as free-floating antibodies. Ehrlich illustrated his proposal with some of the figures reproduced here (fig. 1).

FIG. 1.—Ehrlich's side-chain theory of immunity as diagrammed in 1900. Each cell possesses a number of side chains which bind stereospecifically to toxins. The binding of such toxins causes the overproliferation of that particular side chain, some of which are shed from the cells as antibodies. (Reprinted from [11].)

Here we see the beachhead of stereocomplementarity on biology and medicine, and Ehrlich advertised the importance of stereocomplementarity for scientific pharmacology. "That chemical substances are only able to exercise an action on the tissue element with which they are able to establish an intimate chemical relationship is a conception of a general nature which has been entertained since the birth of scientific medicine. It is astonishing, almost astounding, that this axiom, of which the theoretical importance has been so long recognized . . . should as a matter of fact have played in the building up and furtherance of

scientific pharmacology a *role* so insignificant in proportion to its great importance" [11, p. 429].

It is also interesting that, like the biochemists (and his rival immunologist, Metchnikov), Ehrlich grounds his immunological theories in a nutritional framework. (Ehrlich speculated that the effect of toxins could be abrogated by giving animals more of specific foodstuffs.) Moreover, in this model, antibodies are not the product of a specific group of cells (lymphocytes) but are produced by whatever cell binds the toxin. While several authors have seen in this theory an ancestor of the current clonal selection hypothesis (e.g., [12]), it was not well received in all quarters. De Kruif [13] despaired of it, saying that "to his dying day, Paul Ehrlich believed his silly side-chain theory of immunity." Yet, as we shall see, Ehrlich's speculations were critical for introducing lock-and-key specificity into biology and medicine. The details of his theory, however, were soon shown to be erroneous. The rock on which his theory broke, moreover, was stereospecificity itself. Landsteiner (1935) demonstrated that organisms could produce antibodies to organic molecules which are not toxic and which are not produced in nature. Moreover, Landsteiner showed that the body produced a set of antibodies to *ortho*-substituted benzene rings different from those to *meta*- or *para*-substituted rings. The stereospecificity was far too great and far too diversified for the nutrient side-chain hypothesis.¹

III

Ehrlich had brought stereocomplementarity from the realm of chemical reactions in solution to reactions of the cell surface. Lock-and-key reactions occurring on the cell surface was a new idea which could be used to explain the cell specificity of many reactions, and the notion of stereospecific receptors entered into medicine largely through the pioneering studies of J. N. Langley. Langley's investigations on the effect of curare and nicotine on striated muscle (1905) led to his concluding that there was a specific *receptive substance* in muscles which was not the same as the apparatus required for contraction:

Since, in the normal state, both nicotine and curari abolish the effect of nerve stimulation, but do not prevent contraction from being obtained by direct stimu-

¹The concept of cell-specific binding is paramount in all of Ehrlich's work. The initial phase of his research career dealt with the discovery of stains that would bind to one cell-type only. After his immunological period, Ehrlich's research focused on chemotherapy. Ehrlich's revolutionary drug, Salvarsan, was created in 1910 through his belief that if you coupled a poison to a cell-specific dye, you could direct the poison to kill that cell specifically. Thus, he artificially made a drug composed of a "haptophore" region (dye) and "toxophore" region (poison). The idea of directing drugs to specific cells, coupling them to agents that bind to the cell surface, has recently been revised by monoclonal antibody technologies.

lation of the muscle or by a further adequate injection of nicotine, it may be inferred that neither the poisons nor the nervous impulse act directly on the contractile substance of the muscle but on some accessory substance.

Since this accessory substance is the recipient of stimuli which it transfers to the contractile material, we may speak of it as the *receptive substance* of the muscle. [14]

Langley then linked this finding to the processes of embryonic differentiation: "It follows then that there are considerable differences in the receptive substance in different muscles. And it seems to me probable that we must regard the embryonic muscle protoplasm as forming several receptive substances responsive to different chemical stimuli. . . . The varied effects produced by poisons show that the receptive substance varies in different cells."

Langley speculated that the mode of action of these two drugs is related to their ability to compete with the natural binding substance, which he believes to be adrenaline. Moreover, he hypothesized that hormones, in general, act by binding to specific receptive substances on their target tissues. Here, then, we have the first notion of cell-specific receptor molecules for drugs and hormones. Langley noted the similarity between his views and those of Ehrlich's side-chain theory (which he mentions casually and without reference, assuming them to be well known), but he does not want to get tied down to the controversy surrounding the details of Ehrlich's model: "The relation between the receptive and the contractile substance is clearly very close, and, on the general lines of Ehrlich's immunity theory, it might be supposed that a receptive substance is a side-chain molecule of the molecule of contractile substance, but at present there does not seem to me to be any advantage in attempting to refer the phenomena to molecular arrangement." So by 1905, the idea of stereocomplementarity had been taken from chemistry into medicine. In one remarkable paper, Langley advanced new notions of cell specificity, hormone action, pharmacology, and neuromuscular development. The unifying concept for all these fields was the stereocomplementarity between a cellular receptor and an external compound.

IV

In biology, the lock-and-key hypothesis gained headway through well-publicized experiments in embryology. The discovery that sperm and egg cells interacted to form the zygote was made only as late as the 1870s. This interaction was seen to be specific for these two cells, as sperm did not fertilize other cell types. Fertilization became a model system which embryologists attempted to use to explain how specific

intercellular interactions might guide cell movements during development. Thus, as early as 1910, Ross Harrison [15] postulated that growing axons might attach to their target as the sperm attaches to the egg: "That it must be a sort of a surface reaction between each kind of nerve fiber and the particular structure to be innervated seems clear from the fact that sensory and motor fibers, though running close together in the same bundle, nevertheless form proper peripheral connections, the one with the epidermis and the other with the muscle. . . . The foregoing fact suggests that there may be a certain analogy here with the union of egg and sperm cell."

The nature of these interactions was unknown, but in 1914, Frank Lillie detailed his experiments leading to a new model of fertilization. Lillie [16] postulated that the sperm and egg were linked by stereocomplementary reactions at the cell surface. Just as a cell could bind a certain type of molecule, a cell could bind to certain other cell types. From its original molecule-to-molecule context, the lock-and-key notion now guided hypotheses of cell-cell interactions.

Lillie's fertilization hypothesis borrowed extensively from Ehrlich's model of antibody formation, so much so that Lillie had to apologize for his use of immunological terms: "The terminology has been largely adopted from immunology, because it seemed best suited to express the facts. If it seems rather bizarre to the zoological reader, I must ask him not to conceive prejudice for this reason against the facts themselves. . . ." In particular, the terms were derived from Ehrlich's side-chain theory. The egg, he postulated, produced a substance, *fertilizin*, "possessing two side-chains active in fertilization, viz: one reacting with the sperm which I call the 'spermophile side-chain' or group and the other reacting with the egg which I call the 'ovophile side-chain' or group. The chemical group of the sperm which interacts with the fertilizin is named the sperm receptor and that of the egg the egg receptor." We are not far away from Ehrlich's "toxophile side chain," and like these side chains, fertilizin could exist either within the egg cortex or in a soluble form secreted by the egg.

Not only were Lillie's terms immunological, so were his techniques. If the fertilizin produced by the egg could bind the sperm cells, it could be assayed by agglutination, just as immunologists would assay antibodies against erythrocytes or microorganisms. So Lillie takes pains in his paper to describe the technique of a serial dilution and agglutination assay.

Fertilizin could be extracted from ripe sea urchin eggs by washing them in water, and its concentration could be standardized by examining its ability to agglutinate sperm. Lillie localized it to the egg's jelly coat and to its cortex and found that fertilizin is secreted by the unfertilized eggs, not by fertilized eggs, and that the sperm have a high affinity for this

substance. These facts, combined with the observation that when eggs were repeatedly washed they lost both their fertilizin and their ability to be fertilized, led him to conclude that fertilizin "is essential for fertilization."

Lillie also found that when eggs were deprived of their jelly and agitated until they broke, the fertilizin in the water surrounding the eggs lost its power to agglutinate sperm. He called this substance which neutralizes fertilizin "antifertilizin." It seemed to him likely that this substance functioned as a block to polyspermy.

These facts allowed Lillie to construct his theory of fertilization. In it the ovum produces fertilizin, a compound with a "spermophile" side chain and an "ovophile" side chain. When a sperm receptor united with a fertilizin spermophile group, the fertilizin was activated so that the ovophile group might unite with an egg receptor. This caused the filling of the rest of the fertilizin spermophile groups by antifertilizin molecules; in turn, this prevented polyspermy and formed the fertilization membrane.

Lillie's representation of these interactions is presented in an explicit lock-and-key diagram (fig. 2). In addition, Lillie noted that both his and Ehrlich's models proposed that cellular responses (fertilization, antibody formation) were due to the interaction of preexisting side chains with molecules of particular defined specificity. (To this end, Lillie speculated that sperm from different species probably had different receptor molecules on their surfaces.) Lillie claimed, however, that "to represent them in terms of the Ehrlich hypothesis as definite lock-and-key chemical combinations is of course to go beyond the facts." Yet, he states that this will nonetheless be his working hypothesis.

The fertilizin model is interesting for several reasons. It is the obvious source of several later hypotheses in developmental biology: Weiss and Tyler developed it into a lock-and-key model for cell movements during development; Sperry's chemoaffinity hypothesis and the cell adhesion hypotheses of both Steinberg and Moscona can be traced back to it. In the study of fertilization itself, Lillie's theory presages the bindin-vitelline membrane mechanism proposed during the past 5 years [17]. The fertilizin model is also the first speculation wherein receptor molecules on the cell surface are altered by the binding of their agent, and this alteration enables them to interact with other molecules within the cell; for Lillie speculates that the "union of a sperm receptor with a spermophile group of the fertilizin molecule activates the latter so that the ovophile group forms a union with the egg receptor." Here, then, we see the germ of the allosteric mechanism which will later be used to explain how the binding of hormones or drugs causes the intracellular reactions without the agent entering into the cell.

FIG. 2.—Lillie's side-chain theory of fertilization as diagrammed in 1914. Successive events of fertilization are depicted in panels 1 and 2. Panel 1 shows the positions of the structures before fertilization. In panel 2, the sperm receptor binds to the spermophile group of the fertilizin, activating the ovophile group to bind to the egg receptor. Molecules of antifertilizin combine competitively with this site on other fertilizin molecules to forbid the binding of other sperm. Panels 3–6 detail experimental conditions not pertinent to the present discussion. (Reprinted from [16].)

V. The Controversy within Physiological Biology

The notion of stereospecific structures did not enter biology without a fight. The first 2 decades of this century saw a major struggle in which a mechanistic, physiological biology was attempting to separate itself from the more descriptive biology that had flourished under the aegis of Darwinism. Many of the “physiological” biologists who had just abandoned the morphological tradition were attempting to make their biology as physically and chemically oriented as possible. To these scientists, stereocomplementary structures represented a return to (or at best a compromise with) the old morphological tradition. Rubin [18] has noted that in turn-of-the-century immunology there were “two dominant chemical styles: the structuralist and the physicalist.” These two styles actually polarized the most important biological controversies of the time. The structuralists saw the physiological activities of the cell to be determined by large insoluble compounds having defined shapes, while the physicalists thought that the molar ratios of soluble reactants determined whether or not a biological process occurred.

This argument was paramount in the Wilson-Morgan debates over whether chromosomes controlled heredity and development [19]. Wilson championed the cause of chromosomes, whereas Morgan (before his *Drosophila* studies) argued that chemical reactions occurring in the soluble cytoplasm directed the organism’s phenotype. For example, Morgan claimed that there was no convincing evidence that different chromosomes directed the sexual development of an organism and cautioned his fellow scientists that “sex determination may not be a result of differential nuclear divisions that locate sex determining chromosomes in different cells, but that the process is *chemical* rather than *morphological*” ([20], italics mine).

At the same time, we see this controversy when stereospecific structures are hypothesized for regulating biological phenomena. Chief among Ehrlich’s opponents was Svante Arrhenius, one of the founders of physical chemistry, who sought to apply chemical kinetics to biological problems. He believed that “substances do not react unless they are dissolved” and that antigen-antibody binding was a reversible reaction subject to the mass action laws of physical chemistry. Thus, Arrhenius disagreed with Ehrlich’s notion of a shape-specific insoluble receptor localized on the cell surface. Rather, he felt that antibody-antigen reactions were electrostatic in nature and occurred reversibly in solution [18]. Ehrlich countered that Arrhenius, whose physical chemistry he respected, did not understand biological phenomena where “substances don’t react unless they are fixed” ([13]; in fact, Ehrlich entitled his lecture at The John Hopkins University, “Physical Chemistry versus Biology in the Doctrine of Immunity”).

Arrhenius had an important ally in Jacques Loeb, who was having a similar controversy with Frank Lillie. Loeb was the great popularizer of "the mechanistic view of life" and saw everything save physical chemistry as mysticism. The older generation of biologists, he claimed, "... did not realize that not only the methods of the physicist are needed but also the physicists's general viewpoint concerning the nature of scientific explanation . . ." [21]. Science was only scientific as far as it was mathematical. In a letter to Lillie criticizing the fertilizin hypothesis, Loeb hit not only the experimental data but the structuralist model from which Lillie proceeded. We see here Loeb's intensely mathematical philosophy of science, his distaste for Ehrlich's hypothesis (and for nonmathematical hypotheses in general), and his admiration of Arrhenius's physical chemistry:

I can assure you that there was nothing else on my mind except the discussion of what I consider a hypothesis, in contradistinction from a mathematically formulated theory. I have always been of the opinion that only the latter type of theory has any right to exist in biology as well as in the other sciences. Formerly, before the introduction of physical chemistry into biology and before the ascent of Mendelism, quantitative methods in biology were very rare and in their place we had hypotheses or vague speculation. You remember how during the Darwinian period almost everybody was busy in developing lines of descent for different types of organisms which, of course, were purely hypothetical, could neither be proved nor disproved, and led to no end of polemics and unfortunately also to a great many animosities. This ceased when the mathematically formulated ideas of the Mendelian type replaced the old fashioned evolutionary speculations. We have seen a similar change in the field of medicine when Ehrlich's side-chain theory, which was only metaphorical, was replaced by the quantitative methods of physical chemistry under the leadership of Arrhenius. I feel that the same change will have to come throughout biology and for that reason I consider hypotheses, whether forwarded by myself or by others, as something of only transitory value; though I myself have been guilty of publishing such hypotheses I have almost reached the conclusion that biology might have been able to get along better without them. [22]

Loeb rejected Lillie's own attempts at quantitation and saw Lillie's results as artifacts caused by tiny pieces of jelly which trapped the sperm heads. But what appeared to bother Loeb the most was that Lillie was not dealing with chemical reactions that could be formulated in terms of mathematical equilibria.

Loeb's major contribution to the problems of fertilization was his demonstration of *artificial parthenogenesis*, the activation of the egg to develop onto an organism without being fertilized by sperm:

The question of how a spermatozoon can cause an egg to develop into a new individual was twelve years ago still shrouded in mystery . . . but today we are able to state that the problem of the activation of the egg is for the most part reduced to physico-chemical terms. . . . I succeeded twelve years ago in causing the unfertilized eggs of sea urchins to develop into swimming larvae by treating

them with sea water, the concentration of which was raised through the addition of a small but definite quantity of a salt or sugar. . . . These experiments proved the possibility of substituting physico-chemical agencies for the action of the living spermatozoon. [23]

Sperm was not needed for the creation of a new organism from the egg; magnesium chloride or butyric acid was sufficient. According to Loeb, all the sperm did to activate development was to destroy the cortical layer of the egg. No special morphologically precise binding site was required. Rather, the importance of the sperm consisted in its bringing to the egg those chemicals that would lyse the cortex. Thus, he wrote, "I consider the chief value of the experiments on parthenogenesis to be the fact that they transfer the problem of fertilization from the realm of morphology into the realm of physical chemistry" [24, p. 123]. The title of Loeb's most popular book, *The Mechanistic Conception of Life*, may be a rather apt pun.

Loeb was willing to take on Lillie and at the same time criticize Ehrlich. He stated that not only did Lillie misuse Ehrlich's model of immunity but the model was invalid. In particular, Loeb criticized the notion that the fertilizin was an "amboreceptor," mediating the recognition of sperm and egg, "the latter being the complement, the former the antigen. The pathologist would probably object to this interpretation since no 'amboreceptor' is needed for agglutination" [24]. (Here, Loeb is misreading immunology, for Ehrlich's notion that the antibody had two functional domains, one specifically recognizing an antigen while the other binding complement, was an incredibly accurate prediction and one directly based on his model. Ehrlich and his co-workers were well aware that antibodies bound or activated complement only when they themselves were bound to their targets.) But Loeb was using this to criticize not Lillie but Ehrlich, on whose work Lillie's was based. He stated that he questioned the validity of the side-chain theory and that the ideas of chemical equilibrium found in Arrhenius's *Quantitative Laws in Biological Chemistry* were much more applicable.

We can see, then, that in physiological biology there was a definite split into the chemists (such as Morgan, Arrhenius, and Loeb) and the structuralists (such as Wilson, Ehrlich, and Lillie). Pasteur himself was mindful of these two ways of thinking. One school of thought, he said, used the chemical method, which seeks to study materials by chemically modifying them and studying the resultant products. The other used the physical method, which seeks to look at the external shape of the compounds. "By taste and doubtless also by chance," wrote Pasteur [3, pp. 392–393] "it is this latter method which I have followed especially in my researches, while not at all neglecting the first."

Thus, we have seen how stereocomplementarity, the central unifying notion of modern cellular biology, biochemistry, and medicine, grew

from Pasteur's experiments in organic chemistry to the biological and medical speculations of the first 2 decades of the twentieth century. We see a progression of conceptual leaps in which a hypothesis originally designed for solution chemistry is extrapolated to explain the interaction of the cell surface with soluble molecules and then to explain the reactions of two apposed cell surfaces. In this process, immunology mediated the transfer of the stereospecificity hypothesis from chemistry to biology and medicine.

When the models of Ehrlich and Lillie were criticized as too morphological and not meeting the demands of physical chemistry, the notion that chromosomes controlled development and heredity was also criticized on the same grounds. Thus, in the first 2 decades of this century, the two great paradigms of contemporary development biology—that differentiation is controlled by the expression of nuclear genes, and that morphogenesis is regulated by reactions occurring at the cell surface—were both being formulated and tested. In both cases, a compromise between physical chemistry and morphology was seen to provide the best explanation of the data. So, although the details of Ehrlich's theory of antibody production and Lillie's theory of fertilization have both been disproved, the theories are still correct in their postulating stereospecific interactions at the cell surface, and they played a major role in introducing this concept into biomedical science.

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